

Angiofollicular lymph node hyperplasia (Castleman)

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SYNOPSIS Six personally observed cases of this lesion are reported and the literature is reviewed. One hundred and thirty-four cases have been reported to date. The lesion has occurred in many sites, but is commonest in the thorax (60%), abdomen (11%), neck (14%), and axilla (4%).

Ninety per cent of cases are symptomless or have only the pressure symptoms, 10% have systemic signs, namely, fever, raised ESR, anaemia, cured by removal of the tumour. These cases have a slightly different histology. All recorded cases have been benign. Microscopically the lesion is follicular but instead of germinal centres the follicles have one or more thick-walled arteries and often some surrounding histiocytes. Increased numbers of vessels occur between the follicles, whilst sinuses are absent. These vessels have thick, cellular walls like post-capillary venules. Sometimes they become hyaline.

The cases with symptoms have true reaction centres as well as a few intrafollicular vessels. Between the follicles there are increased numbers of vessels and, in addition, there may be collections of plasma cells or eosinophils.

In 1954 and 1956 Kane *et al.*, and Castleman, Iverson, and Menendez, described 13 cases of intra-thoracic lymphoid tumours with a benign behaviour. They regarded them as lymph node hyperplasias and were at pains to distinguish them from thymomas. Since then numerous cases have been reported, but surprisingly very few in British literature. For this reason it seems justifiable to report six new cases and to draw attention to the diagnostic features.

Case 1

A man of 32 attended hospital complaining of asthma. A chest radiograph showed a rounded shadow just above the right hilum. Two years later a thoracotomy was performed and a rounded mass was removed from immediately above the right stem bronchus. Recovery was uneventful and the patient's asthma was cured. He was well 14 years later.

Case 2

A woman of 21 was found on mass radiography to have a rounded shadow just above the left hilum. At thoracotomy a chestnut-sized mass was found

among the branches of the left pulmonary artery and between the bronchi. This was removed. The patient was well six years later when she emigrated to Canada.

Case 3

A man of 43 complained of a lump in his neck. He had noticed it for a year but recently it had become painful and had sometimes caused earache. The lump lay behind the upper part of the sternomastoid. At operation a rounded mass was found adherent to the carotid sheath. It was dissected free. The patient was well seven years later.

Case 4

A man of 38 was referred to hospital because of a shadow seen on routine chest radiography. He was stated to have had a similar shadow 10 years previously, but the films were no longer available. At thoracotomy a rounded mass 4 cm in diameter was found applied to the posterior wall of the left lower lobe bronchus. The tumour and the left lower lobe were removed. The patient was well nine years later.

Case 5

A woman of 53 gave a four-year history of attacks of

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pain along the left costal margin sometimes radiating to the breast and left arm. The attacks occurred three to four times a day. The only positive finding was a rounded shadow on chest radiographs, situated in the left upper mediastinum close to the aortic arch. At operation a lobulated, encapsulated mass 10×5 cm was found adjacent to the arch of the aorta and pulmonary artery. It was excised and the pain disappeared. She was well and free from pain four years later.

Case 6

A woman of 61 was admitted in 1967 and gave a history that, 25 years before, whilst being treated for dysentery in India she was found to have an abdominal mass. A tumour was removed from the bifurcation of the aorta and she was given deep x-ray therapy. The nature of this tumour could not now be ascertained. In 1958 she developed intestinal obstruction due to diverticulitis necessitating resection of a segment of colon. In 1967 she developed constipation due to diverticulitis, and whilst being investigated for this was found to have anaemia, raised sedimentation rate, and an abnormal chest radiograph and she was referred to Dr Brain at Hammersmith Hospital. She was fully investigated and the following were the positive findings: fever up to 99.4°F ; Hb 9.6 g.; PCV 33%; MCHC 29%; platelets 485 000/cmm, wbc 8 000/cmm. Bone marrow showed signs of iron deficiency and mild megaloblastic change. Alkaline phosphatase 13 to 24 King-Armstrong units. Serum proteins, albumin 2.7 g, globulin 3.1 g, later albumin 2.2 g, globulin 5.3 g, ESR varied between 99 mm and 124 mm/hr; serum iron $10 \mu\text{g}/100$ ml, serum folate $4.8 \mu\text{g}/\text{ml}$. A chest radiograph showed a shadow in the right paratracheal region displacing the trachea slightly to the left. It was considered that this was a malignant lymphoma and was the cause of her illness, and two attempts were made to establish a histological diagnosis, first, by a scalene node biopsy and secondly by mediastinoscopy with lymph node biopsy. Both yielded histologically normal lymph nodes. Finally, on 22 November 1967 a thoracotomy was performed and a large smooth mass was found occupying the right side of the superior

mediastinum. This was removed piecemeal. Following the operation the ESR fell to 8 mm and later to 5 mm/hour. She was treated with iron and folate and discharged. A year later her haemoglobin was 13.0 g/100 ml and serum proteins were 7.2 g/100 ml (albumin 3.5, globulin 3.6). She was well, apart from occasional attacks of cystitis. At a recent follow up nearly four years after operation she was still well.

Histology

The main histological points are summarized in Table I. In all six cases the specimen consisted of lymphoid tissue with prominent lymphoid follicles. These follicles had a mean diameter between 355 (case 3) and 480μ (case 6). (The follicles in six cases of reactive follicular hyperplasia had a mean diameter of 610μ .) These follicles were crowded together with little space between them in cases 1 and 5, but in the other four had spaces between them equal to 1 or 2 follicular diameters. There were foci of pale cells in the centres of the follicles (Fig. 1). These were present in roughly half the follicles of cases 1 to 5 and were small and had mean diameters between 65 and 80μ . In case 6 (Fig. 4) they were larger with a mean diameter of 200μ and were present in most of the follicles. The pale reaction centres in six control cases of reactive follicular hyperplasia had a mean diameter of 380μ . In all cases the follicles were composed of well differentiated lymphocytes and were sometimes arranged in concentric rows like strings of beads (cases 2, 4, and 5). Within the follicles in cases 1-5 thick-walled arterioles were easily seen in ordinary preparations and were obvious in reticulin preparations (Fig. 2). Sometimes these ran radially, sometimes they turned and part lay parallel to the circumference. In cases 1, 2, and 5 these vessels were often hyaline (Fig. 3), and a few were hyaline in case 6. The pale areas in the centres usually consist of an extension of the thick intra-follicular vessels surrounded by small clusters of histiocytes. In cases 3 and 5 there were, in addition, a few true reaction centres. Although these reaction centres contained some mitotic figures they did not show phagocytosis. Case 6 showed some differences. Most of the lymphoid follicles had pale centres and

Case	Mean Follicle Size (μ)	Pale Centres in Follicles (size μ)	Frequency of Pale Centres	Hyaline Strands in Follicles	Hyaline Strands between Follicles	True Reaction Centres	Mitoses
1	400	70	10/20	+	+	—	—
2	380	70	10/20	+	+	—	—
3	355	80	12/20	—	—	One seen	\pm
4	400	65	10/20	—	—	—	\pm
5	400	80	8/20	+	+	Two seen	+
6	480	200	17/20	\pm	—	Majority	+

Table I Summary of histology of present series

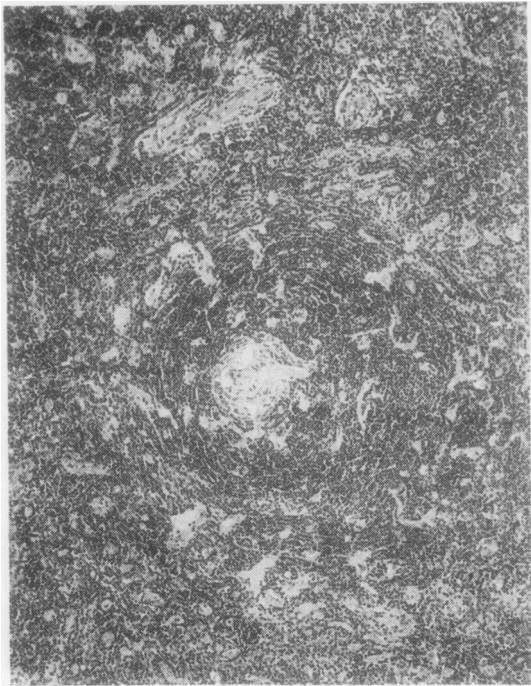


Fig. 1 Case 5. Typical follicle showing central pale area with an artery entering from the right, numerous pale staining vessels within and around the follicle. *H & E* $\times 100$.

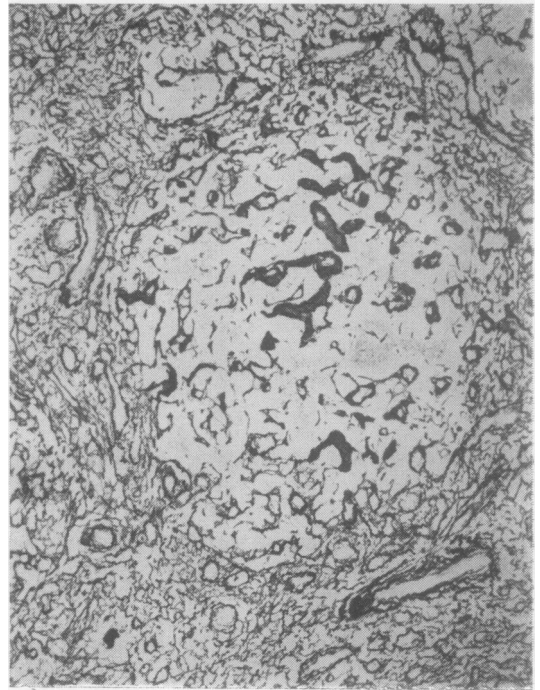


Fig. 2 Case 5. Reticulin preparation showing numerous vessels within a follicle and also between follicles. *Gordon & Sweet's method*. $\times 100$.

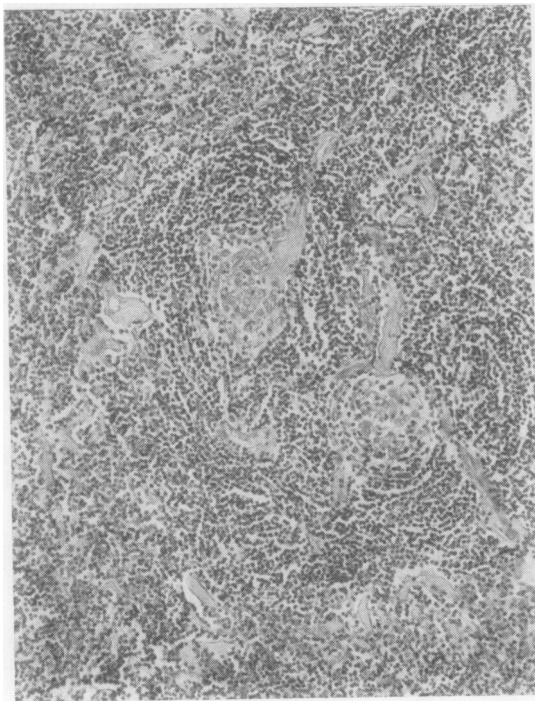


Fig. 3 Case 1. A follicle with two pale centres each entered by a hyaline vessel from above. Similar hyaline vessels are seen outside the follicle. *H & E* $\times 150$.

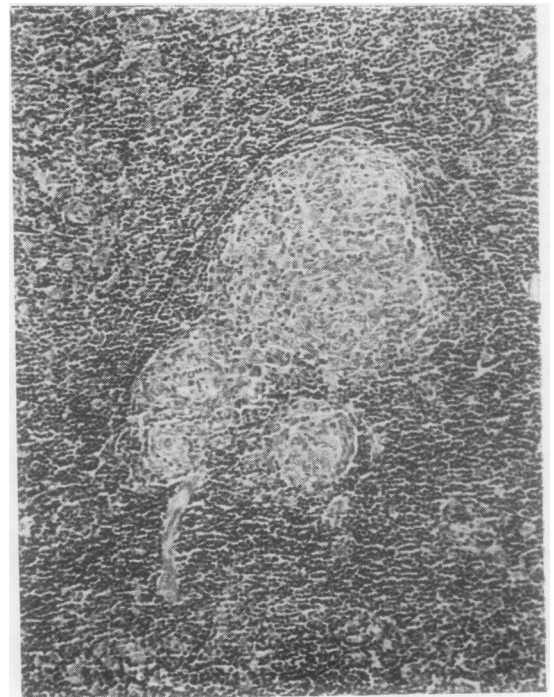


Fig. 4 Case 6. Central part of a follicle showing two pale centres, one of irregular shape. A single vessel enters at the bottom. *H & E* $\times 150$.

these were often irregular in outline and sometimes multiple (Fig. 4). They mostly resembled ordinary reaction centres, though phagocytosis was scanty or absent. Pale centres with visible arterioles of the type seen in the other five cases were scanty and the arterioles were less prominent.

In all six cases the interstitial tissue between the follicles had a reticulin framework in the form of a regular meshwork essentially like that of a normal lymph node, but with no visible sinuses and with excessive numbers of blood vessels. The cell population consisted largely of small lymphocytes with a smaller number of histiocytes and a few eosinophils. Case 6 was peculiar in showing large numbers of eosinophils and large numbers of plasma cells, usually in separate areas. In all cases the numerous blood vessels seen in reticulin preparations had thick cellular walls like post-capillary venules. Sometimes these had become fibrous and hyaline (cases 1, 2, and 5). In addition, there were often muscular-walled arteries, more numerous than are seen in normal lymph nodes. In cases 3 and 5 a portion of normal lymph node was present at the margin. These contained normal sinuses but these did not penetrate into the lesion. In case 5 the normal portion contained carbon, but none was present in the lesion.

Diagnosis

The early workers (Castleman *et al*, 1956; Abell, 1957) were concerned to differentiate this lesion from thymoma because of a supposed resemblance between hyaline foci in the follicles and Hassall's corpuscles. In practice these lesions are much more likely to be mistaken for either follicular hyperplasia or follicular lymphoma. In the typical cases (1-5) the thick-walled and sometimes hyaline arterioles within the follicles are so characteristic that the diagnosis is not difficult once its possibility is realized. In examples like our case 6 the differentiation from follicular hyperplasia is difficult. The points that were helpful were the irregular outline of the pale centres, the presence of abnormal vessels in some of them, and the failure to find sinuses in the intervening tissue. The presence of numerous plasma cells is of no diagnostic help, but the presence of quite heavy concentrations of eosinophils is not usual in either follicular hyperplasia or follicular lymphoma and might, therefore, alert one to the possibility of this lesion.

Discussion

Since Castleman's original publication there have been numerous case reports and several series of

cases. It has become apparent that this lesion is not limited to the thorax and that it can be associated with generalized signs and symptoms not related to a space-occupying lesion. In 1967 Tung and McCormack reported five new cases and reviewed the literature, tabulating 64 cases in all and including four described before Castleman's publication. In 1969 Flendrig reported 13 new cases from Holland and again reviewed the literature. He excluded four of the early cases quoted by Tung and McCormack and accepted 111 cases in all. Since then we have found a further 17 published cases and add six new ones, bringing the total to 134. The sexes are equally affected—67 males and 67 females. The age is from childhood to the seventh decade, the great majority occurring between 10 and 45. The site of the lesion is given in Table II. It will be seen that 84 out of 134 cases occurred within the thorax, 15 within the abdomen, and 24 in the neck or axilla. The other 10 occurred in sites where lymph nodes would not ordinarily be expected. It appears, therefore, that this lesion may be encountered in almost any site but that the thorax, abdomen, neck and axilla are sites in which the great majority will occur.

Anterior mediastinum	22	} 84
Posterior mediastinum	21	
Mediastinum	6	
R hilum	24	
L hilum	11	
Retroperitoneum	9	} 15
Mesentery	5	
Lateral pelvis	1	
Neck	19	
Axilla	5	
Dorsal chest wall	1	
Abdominal wall	1	
Among muscles	3	
Around shoulder	3	
Larynx	1	
Vulva	1	
Floor of mouth	1	
Total	134	

Table II Site of tumours

Flendrig (1969) drew special attention to the occurrence of symptoms and divided his own and the published cases into two groups. Ten of his cases and 91 published cases had either no symptoms or only those associated with the presence of a space-occupying lesion. Three of his cases and seven published cases had other systemic signs and symptoms that disappeared after the removal of the tumour. We have found two further published cases and add one more (our case 6). Flendrig lists the findings as fever, enlarged lymph nodes in other parts, splenomegaly, anaemia with decreased serum iron

and decreased iron-binding capacity, leucocytosis, thrombocytosis, raised sedimentation rate, low serum albumin and raised globulin, increased fibrinogen and raised alkaline phosphatase, and an excess of plasma cells in the bone marrow. After removal of the tumour these symptoms and signs 'disappeared remarkably fast and completely'. In these cases the histology of the excised lesion was slightly different. There was the same excess of small vessels between the follicles, but there were numerous true reacting follicles with germinal centres. These did not contain proliferating vessels or hyaline strands. There was, in addition, a heavy infiltration of plasma cells between the follicles. The descriptions of the histology given by Lee, Rosner, Rivero, Feldman, and Hurwitz (1965); Helsing and Mylius (1967); Lüthi, Sordat, and Büttler (1968); and Neerhout, Larson, and Mansur (1969) are all of this type and all in patients cured of their symptoms or signs. Our case 6 corresponds both clinically and morphologically to Flendrig's second group.

The nature of the lesion is unknown. That it is benign is apparent from all published reports. It was thought to be reactive, but no cause for an inflammatory reaction has been discovered, and in any case the follicles are morphologically different from those of true follicular hyperplasia. The continuity of the lesion with normal node in a number of cases suggests that it is of lymph node origin in spite of the situation of some lesions. The abnormal vascular pattern and the absence of normal sinuses is consistent with either a benign tumour or with a hamartoma, and some authors have used the latter term. In the present state of ignorance it is probably wiser to use the descriptive title 'angiofollicular lymph node hyperplasia'. Whether, in the light of Flendrig's separation of cases into two clinical and morphological groups, this will prove to be two diseases or one it is too early to say, but Krasznai and Juhász (1969) describe a case cured of thrombopoenia whose lesion appears to correspond with the symptomless type. Certainly until more is known about this lesion it is wiser to document all cases together.

The literature was fully reviewed by Tung and McCormack up to 1967. Because the excellent review by Flendrig is in Dutch and is not readily available we have listed all the publications since Tung and McCormack's paper.

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